# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ROBERT A. GOETZ
MEDLEN & CARROLL, LLP
101 HOWARD STREET, SUITE 350
SAN FRANCISCO, CA 94105

# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

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|---|---|
| Date of mailing (*day/month/year*) | 03 NOV 2005 |
| Applicant's or agent's file reference<br>UM-09484 | FOR FURTHER ACTION<br>See paragraph 2 below |

| International application No. | International filing date (*day/month/year*) | Priority date (*day/month/year*) |
|---|---|---|
| PCT/US05/01363 | 18 January 2005 (18.01.2005) | 16 January 2004 (16.01.2004) |

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 38/05, 38/06; C07K 5/062, 5/083 and US Cl.: 514/18, 19; 530/331; 540/484; 544/1; 546/245; 548/100, 530, 953

Applicant

THE REGENTS OF THE UNIVERSITY OF MICHIGAN

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| | |
|---|---|
| Name and mailing address of the ISA/ US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Jeffrey E. Russel<br>Telephone No. (571) 272-1600 |

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/01363

**Box No. I Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/01363

**Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims 27-30 | YES |
| | Claims 1-26 | NO |
| Inventive step (IS) | Claims NONE | YES |
| | Claims 1-30 | NO |
| Industrial applicability (IA) | Claims 1-30 | YES |
| | Claims NONE | NO |

2. Citations and explanations:

Claims 1, 2, 4, 5, 7, 8, 10-14, and 16-24 lack novelty under PCT Article 33(2) as being anticipated by Wang et al. Wang et al teach Hid-4/SEQ ID NO:15, which corresponds to Applicant's Formula I in which $R_1$ is $C_1$ alkyl, $R_2$ is branched alkyl, Y is $CH_2$, Z is CONH, and $R_3$ is substituted alkylaryl. The compounds of Wang et al are apoptosis enhancers, and are administered in combination with chemotherapeutic agents or radiation in order to treat cancer. See, e.g., the Abstract; column 11, line 43 - column 12, line 9; Table 4; and claims 2-6.

Claims 26-30 lack an inventive step under PCT Article 33(3) as being obvious over Wang et al. Application of Wang et al is the same as in the above paragraph. Wang et al do not teach their apoptosis enhancers in kit form in combination with chemotherapeutic agents and instructions for use. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to package the apoptosis enhancers of Wang et al in kit form with the chemotherapeutic agents of Wang et al and with instructions for use, because kits comprising therapeutic agents and instructions for use are commonly used in the therapeutic arts for ease of storage, transportation, measurement, and administration.

Claims 1-12, 14-17, and 19-26 lack novelty under PCT Article 33(2) as being anticipated by Novartis Pharma GMBH. Novartis Pharma GMBH teaches XIAP inhibitors used to treat proliferative disorders, including cancer. The XIAP inhibitors can be packaged in containers, ampules, and vials. Examples 2-6 of Novartis Pharma GMBH meet the requirements of Applicant's Formula I, and in particular Example 2 of Novartis Pharma GMBH is the same compound as is recited in Applicant's claim 3, page 70, line 1. See also, e.g., the Abstract; page 10, lines 12-13; and page 11, line 25 - page 12, line 14.

Claims 27-30 lack an inventive step under PCT Article 33(3) as being obvious over Novartis Pharma GMBH. Application of Novartis Pharma GMBH is the same as in the above paragraph. Novartis Pharma GMBH does not teach the apoptosis enhancers in kit form in combination with chemotherapeutic agents and instructions for use. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to package the apoptosis enhancers of Novartis Pharma GMBH in kit form with the chemotherapeutic agents of Novartis Pharma GMBH and with instructions for use, because kits comprising therapeutic agents and instructions for use are commonly used in the therapeutic arts for ease of storage, transportation, measurement, and administration.

Claims 1-30 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry. The claimed invention would have been expected to have industrial applicability in the therapeutic induction of apoptosis and the treatment of cancer.